Intravesical therapy use in the high risk patient: practice patterns in an equal access healthcare institution before and after national guidelines

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Purpose: *We examined patterns of intravesical therapy use in nonmuscle invasive bladder cancer over the last 10 years at our institution where there is equal access to healthcare. We further examined any affect that the introduction of national guidelines may have had on the utilization of intravesical therapy in these patients.*

Materials and methods: *An Institutional Review Board (IRB) approved retrospective chart review was performed between the years 1997 and 2007. Only those with premalignant or malignant pathology, as identified using intradepartmental surgical logs and pathology reports, were included.*

Results: *Four hundred seventeen procedures, representing 228 patients, were identified that met the above criteria. A total of 170 high risk, nonmuscle invasive bladder tumors (HG, CIS and T1) were identified, or 41% of cases in whom intravesical therapy was indicated according to the 1999 American Urological Association (AUA) guidelines. One hundred nine (64.2%) received intravesical therapy and 61 (35.8%) did not. This corresponds to an underutilization rate of 19.4% (33/170 high risk tumors did not receive intravesical therapy for unknown reasons).*

Conclusions: *We have determined that the utilization of intravesical therapy in patients with high risk nonmuscle invasive bladder cancer has improved since the introduction of the 1999 AUA guidelines in an equal access healthcare institution and that patients are compliant with this therapy.*

Key Words: bladder cancer, intravesical therapy, Bacillus Calmette-Guérin

Introduction

Bladder cancer is the fourth most common cancer in men accounting for 6.6% of all cancer cases and it is the ninth most common cause of cancer in women.[1]

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The number of bladder cancers diagnosed annually in the United States increased by over 50% between 1985 and 2005 and at a 25% faster rate in men than in women.[1] It accounts for 3.0% of all cancer deaths in men and 1.5% in women.[2] Bladder cancer that has not invaded the detrusor muscle is termed nonmuscle invasive transitional cell carcinoma. These lesions can be low grade (less aggressive), high grade (more aggressive), carcinoma in-situ (most aggressive) or can invade into the muscularis mucosa (T1). Approximately 70% of bladder tumors are nonmuscle invasive at presentation.[3]

Recurrence is common in all patients with nonmuscle invasive bladder cancer. Patients with high grade superficial tumors have a high likelihood of recurrence

and higher chances of developing invasive and metastatic disease than do those with low grade superficial tumors.[4] Bacillus Calmette-Guérin (BCG) is an attenuated mycobacterium that was developed as a vaccine for tuberculosis and has been found to have antitumor activity in bladder cancer. After transurethral resection of a bladder tumor, a 6 week course of intravesical BCG (once a week for 6 weeks) has been found to decrease tumor recurrence by 30%.[5] BCG has also been found to reduce the risk of progression, specifically when used on a maintenance schedule. The Southwest Oncology Group (SWOG) reported that in patients who received a 6 week induction course of BCG followed by three weekly instillations at 3 and 6 months and every 6 months thereafter for 3 years had a median recurrence free survival of 76.8 months versus 35.7 months in the control arm.[6]

In 1999, guidelines were published by the American Urological Association (AUA) regarding the use of intravesical therapy (BCG once a week for 6 weeks) in the treatment of nonmuscle invasive bladder cancer.[7] Based on the results of this meta analysis, these guidelines recommended adjuvant intravesical therapy in all patients with high risk, nonmuscle invasive bladder cancer (high grade (HG), carcinoma in-situ (CIS) and T1). Despite these guidelines, a recent study by Huang et al, based on results from the Surveillance, Epidemiology and End Results Program 2003 Patterns of Care Project, found that intravesical therapy is largely underused in patients with high risk nonmuscle invasive bladder cancer on a national level.[8]

Utilization rates of intravesical therapy, specifically BCG, are currently unknown at Madigan Army Medical Center in the treatment of nonmuscle invasive bladder cancer. It is also unknown if utilization rates changed after the introduction of the American Urological Association guidelines on the topic in 1999. Through this retrospective chart review, an ACGME mandated quality improvement project, we aim to define patterns of care at our center and to define these patterns before and after the introduction of the 1999 guidelines in order to determine if the standards of patient care in this disease process are being met. This could ultimately improve patient outcomes at our center in primary bladder cancers.

Methods

An Institutional Review Board (IRB) approved retrospective chart review was performed between the years 1997 and 2007. All patients who underwent transurethral resection of a bladder tumor (TURBT) or bladder biopsy and had premalignant or malignant pathology, as identified using intradepartmental surgical logs and pathology reports, were included. Patients with benign pathology were excluded. Inpatient and outpatient paper and electronic records were reviewed as well as pathology reports and genitourinary tumor board records. We collected data points such as demographics, date of surgery, pathology, use and type of intravesical therapy, number of courses, compliance, interruptions in therapy and reasons for not using intravesical therapy when indicated. Statistical analysis was carried out using SIS software.

Results

We identified 808 procedures (TURBT or bladder biopsy) over the 10 year period, 391 (48.4%) of which returned benign pathology results and were excluded. The remaining 417 (51.6%) procedures, representing 228 patients, returned pathology results consistent with papillary urothelial neoplasm of low malignant potential (PUNLMP) in 30 (7.2%), low grade (LG) Ta in 181 (43.4%), LG T1 in 9 (2.2%), HG Ta in 63 (15.1%), CIS in 47 (11.3%), HG T1 in 51 (12.2%), HG T2 in 27 (6.5%), HG T3 in 2 (0.5%) and nontransitional cell tumors in 7 (1.6%). These findings represent a total of 170 high risk, nonmuscle invasive bladder tumors (HG, CIS and T1) or 41% of cases in whom intravesical therapy was indicated according to the 1999 AUA guidelines.

Of the 170 high risk tumors, 109 (64.2%) received intravesical therapy and 61 (35.8%) did not. One hundred eight of those who received intravesical therapy were prescribed 6 weeks of BCG and one was prescribed 6 weeks of mitomycin. Of the 61 high risk tumors that did not receive intravesical therapy, 17 (27.9%) proceeded to radical cystectomy, 4 (6.6%) had metastatic disease, 3 (4.9%) had a concurrent terminal illness, 2 (3.3%) underwent partial cystectomy and chemotherapy, 1 (1.6%) elected no further treatment, 1 (1.6%) was a poor candidate for intravesical therapy and 33 (54.1%) did not receive intravesical therapy for unknown reasons. This corresponds to an underutilization rate of 19.4% (33/170 high risk tumors did not receive intravesical therapy for unknown reasons).

In evaluating compliance with intravesical therapy, we found that of the 109 tumors that went on to receive intravesical therapy, 44 (40%) had inadequate medical records for review. In the remaining 65 (60%), 61 (93.8%) completed all six courses of therapy and 4 (6.2%) did not. Of those that did not complete intravesical therapy, 1 (25%) elected to undergo cystectomy, 1 (25%) developed BCG sepsis, 1 (25%) stopped treatment for a urinary tract infection (UTI) and never restarted, and 1 (25%) developed hematuria that precluded continuation of therapy.

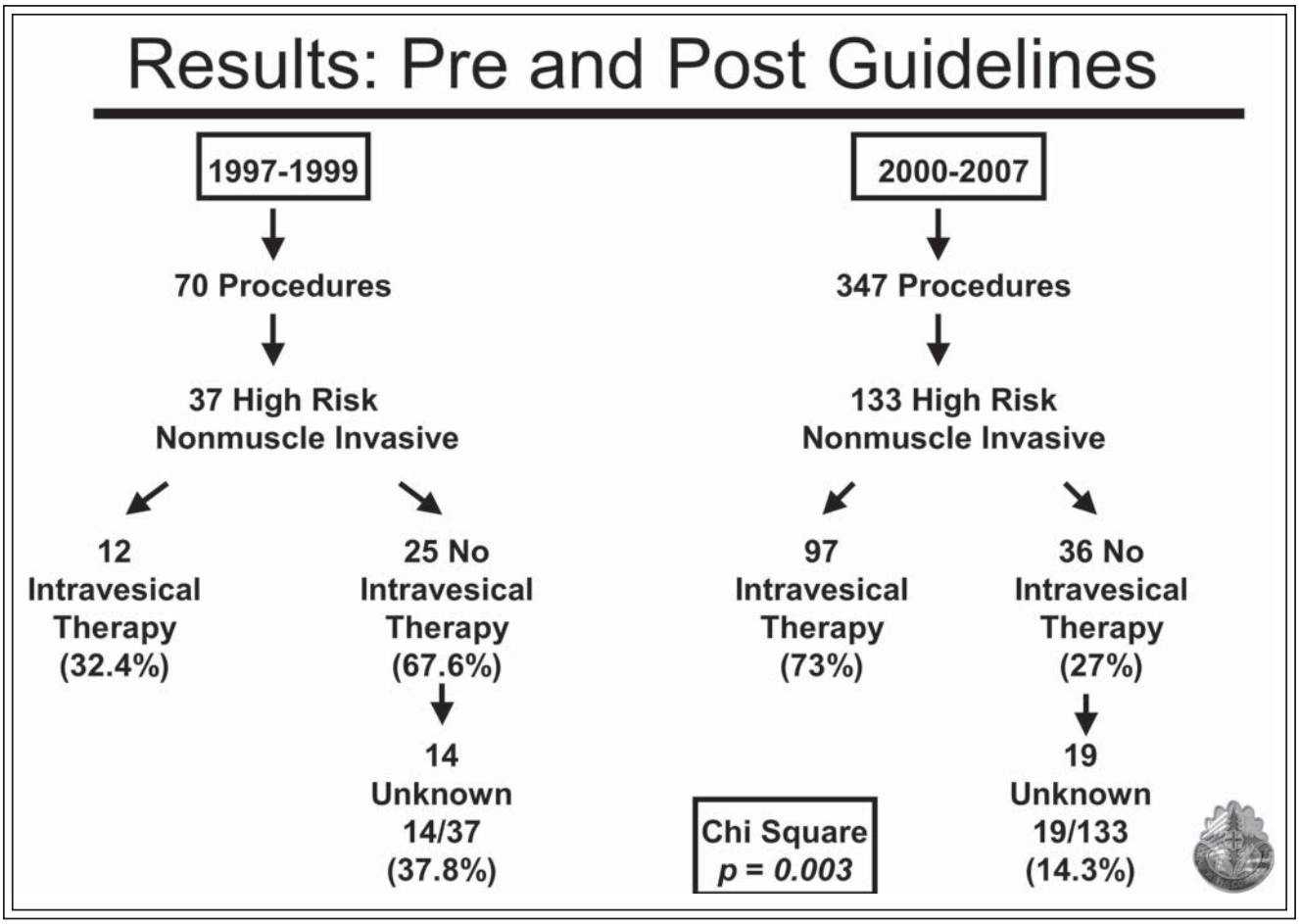

Figure 1. Underutilization rates of BCG prior to and after the 1999 guidelines.

In evaluating interruptions in therapy, 18 (27.6%) of the 65 who received intravesical therapy and had adequate records for review experienced delays in one or more of 6 weeks of therapy. Eleven (61%) were delayed for positive urine dip or microscopy (positive nitrate, leukocyte esterase or bacteria seen on microscopy), 1 for traumatic catheterization, 1 for gross hematuria, 1 for a false passage on catheter placement, 2 were delayed for re-resection of the primary tumor, 1 was delayed by the patient and 1 was delayed for unknown reasons. Of the 11 (61%) who were delayed for positive urine microscopy, 3 had documented UTI's (27%) and 8 did not (73%).

Use of intravesical therapy was also evaluated before and after the introduction of the 1999 AUA guidelines. Between the years 1997 and 1999, 70 procedures were identified (TURBT's and bladder biopsies). Of these, 37 (52.9%) had high risk nonmuscle invasive (HG, CIS, T1) pathology. Twelve (32.4%) received intravesical therapy and 25 (67.6%) did not. Of these 25, 14 (56%) didn't receive the therapy for unknown reasons corresponding to an underutilization rate of 37.8% (14/37 high risk nonmuscle invasive tumors). Between the years 2000 and 2007, 347 procedures were identified, 133 (38.3%) of which had high risk nonmuscle invasive tumors. Ninety seven of them received intravesical therapy (73%) and 36 did not (27%). Of those that did not, 19 (52.8) were for unknown reasons corresponding to an underutilization rate of 14.3% (19/133 high risk nonmuscle invasive tumors). There was a statistically significant difference between underutilization rates with an improvement in utilization after the introduction of the 1999 AUA guidelines ($p = 0.003$, Chi square).

On univariate analysis, higher age was independently associated with intravesical therapy use (70.7 years versus 68.3 years, $p = 0.045$, t-test). Higher grade and stage were also independently associated with intravesical therapy use ($p = < 0.0001$, Mann-Whitney U), Figure 1.

Multivariate analysis could not be performed due to limitations in sample sizes.

Discussion

BCG is a cost effective, well established form of intravesical immunotherapy and is more effective then intravesical chemotherapy at preventing recurrences and progression in nonmuscle invasive bladder cancer.[9,10] Overall recurrence rates for high risk patients are 34% after TURBT and induction BCG compared to 60% after TURBT alone.[11]

In 1999, the AUA released guidelines on the topic.[7] Recommendations were assigned three levels of flexibility: option being the most flexible, guideline being less flexible, and standard being the least flexible. Specifically, the following guidelines were released: 1) Option: adjuvant intravesical chemotherapy or immunotherapy is an option for treatment after endoscopic removal of low-grade Ta bladder cancers; 2) Guideline: intravesical instillation of either BCG or mitomycin C is recommended for treatment of CIS and for treatment after endoscopic removal of T1 tumors and high grade Ta tumors; 3) Option: further intravesical therapy may be considered as an option for patient with CIS or high-grade T1 cancers that have persisted or recurred after an initial intravesical treatment.

Despite these specific recommendations, Huang et al reviewed data from the Surveillance, Epidemiology and End Results Program 2003 Patterns of Care Project including subjects with newly diagnosed nonmuscle invasive bladder cancer in 2003 and found that of the 685 patients included in the study, 350 had high risk nonmuscle invasive bladder cancer. Only 42% received intravesical therapy. Stage, grade, race and geographic location were independently associated with intravesical therapy use suggesting underuse of intravesical therapy in patients at high risk for recurrent and progressive disease. It also suggested disparities in the quality of care across patient groups.[8]

Given these results, we sought to define patterns of care at our center (an equal access health care institution) and to determine if patterns of care changed after the institution of the 1999 AUA guidelines. While we were unable to assess usage of single dose mitomycin due to limited documentation, we found an improved, but significant rate of underutilization of 6 week courses of intravesical therapy in patients with high risk nonmuscle invasive bladder tumors since introduction of the guidelines (37.8% to 14.3%). While it is possible that this retrospective review could have underestimated usage rates due to these limitations in documentation, this is a significant enough number of high risk patients who were not documented to have received the appropriate therapy to inspire us to implement a change in the way we manage and document our management of these patients. This information further suggests that national specialty guidelines do have a role in influencing patterns of care.

We were also able to determine that patients are 93.8% compliant in completing intravesical therapy when it is prescribed. We suspected at the onset of our review that we would identify several patients who did not complete therapy due to side effects, but this was not the case. The AUA reviewed complications reported with the treatment of nonmuscle invasive bladder cancer using both randomized controlled trials and nonrandomized trials.[11] Lower urinary tract symptoms were the most common side effects reported after TURBT and BCG induction (38%). Other symptoms such as hematuria, prostatitis and bladder pain were common as well. Systemic complications were rare, but more common with BCG than other treatment options. Only a few studies in this meta analysis were identified which addressed the number of patients who discontinued therapy due to side effects. From the available data, the panelists concluded that patient discontinuation appears to be relatively uncommon, but commented that in their experience, it occurs fairly frequently, especially with immunotherapy agents like BCG.[11] We have found, in our patient population, that patient discontinuation of intravesical therapy is quite rare and that, overall, it seems to be a well tolerated. In those patients who cannot tolerate intravesical BCG therapy, another option is to decrease the dose of BCG. However, it is unknown if this reduces efficacy.

In evaluating interruptions in the 6 weeks of intravesical therapy, we found that the most common reason for a delay was a positive urine dip or microscopy finding. Documentation regarding which patients were symptomatic in this retrospective review was sparse, but we were able to determine that a small percentage of these patients actually had a documented UTI (27%). This indicates that 73% of patients who experienced a delay, may have experienced this delay unnecessarily. In order to minimize interruptions in therapy for clinically insignificant urine dip findings, we propose to only delay therapy for those with symptomatic urine dip or microscopy findings and to ensure that a urine culture get sent on these patients prior to initiating therapy.

On univariate analysis, intuitively, higher grade and stage were independently associated with intravesical therapy use. We also found that older age was associated with its use. Given this finding, we assessed whether younger patients were being selected for radical cystectomy and whether older patients were being managed with bladder preserving therapies. We did not find a significant difference in age when comparing these groups of patients.

Conclusions

We have determined that the utilization of intravesical therapy in patients with high risk nonmuscle invasive bladder cancer has improved since the introduction of the 1999 AUA guidelines, but that urologists should continue to strive to decrease the current underutilization rates. We have also determined that patients are compliant with intravesical therapy. The most frequent reason for a delay in therapy was found to be concerning preprocedure urine dip results. Interruptions in therapy may be decreased by only delaying treatments for those with symptomatic urine dip and/or microscopy. With the implementation of the newer 2007 AUA guidelines, which focuses on the use of intravesical therapy in recurrent LG Ta tumors, maintenance intravesical therapy and intravesical interferon alpha-2b, we expect to see further improvements in utilization rates, patient outcomes and quality of care. □

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